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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,484	RIDDER ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-37,39,40 and 52-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-37,39,40 and 52-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed July 18, 2007, is acknowledged and has been entered. Claims 1-32 and 41-51 have been cancelled. Claims 33-35, 39, and 40 have been amended. Claims 52-55 have been added.

2. Claims 33-37, 39, 40, and 52-55 are pending in the application and are currently under prosecution.

Grounds of Objection and Rejection Withdrawn

3. Unless specifically reiterated below, Applicant's amendment and/or arguments filed July 18, 2007, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed April 4, 2007.

Response to Amendment

4. The amendment filed July 18, 2007, is objected to under 35 U.S.C. § 132(a) because it introduces new matter into the disclosure. 35 U.S.C. § 132(a) states no amendment shall introduce new matter into the disclosure of the invention. The added material, which is not supported by the original disclosure, includes any and all references to SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 9, 8, 10, 11, 12, 13, and 14, including the substitute Sequence Listing.

Applicant has contended support for the added material is found in a printout from the NCBI website, which is attached to the amendment filed July 18, 2007.

However, written support for the added material must be found in the specification, including the claims, as originally filed; in this instance, it is not immediately apparent where in the specification, as filed, that support may be found.

What nexus between the material, which has not been added to the specification, and information extracted from the NCBI website is found in the specification, as filed?

It is noted, for example, that while it may be Applicant's position that written support for the addition of the sequence set forth as SEQ ID NO: 9 may be found in the

non-patent publication cited in Table 1 (page 21 of the specification, as filed), this disclosure and reference to this publication does not appear to provide support for the added material because it does not *particularly* identify the added material.

According to M.P.E.P. 608.01(p):

> Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. *In re de Seversky*, 474 F.2d 671, 177 USPQ 144 (CCPA 1973).

With regard to incorporation by reference, the Federal Circuit in deciding *Advanced Display Systems Inc. v. Kent State University,* 54 USPQ2d 1673 (CA FC), has further opined:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. *See In re Seversky,* 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-03, 170 USPQ 213, 216-17 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order have that material considered part of a later application); *cf. Lund*, 376 F.2d at 989, 153 USPQ at 631 (holding that a one sentence reference to an abandoned application is not sufficient to incorporate material from the abandoned application into a new application). Whether and to what extent material has been incorporated by reference into a host document is a question of law. *See Quaker City Gear Works, Inc. v. Skil Corp.*, 747 F.2d 1446, 1453-54, 223 USPQ 1161, 1166 (Fed. Cir. 1984) (reasoning that whether a document is incorporated by reference into a patent presents a question of law when determining enablement). *Id.* at 1679-1680.
>
> [Thus] the standard of one reasonably skilled in the art should be used to determine whether the host document describes the material to be incorporated by reference with sufficient particularity. *Id.* at 1680.

In this instance, the disclosures and references cited in Table 1, for example, might be deemed to provide support for the added material *upon proper incorporation by reference of the specific material, which has been added*, but then only if that

amendatory material may be unambiguously identified, upon a reading of the publication, as the particular material that was intended to have been incorporated by the original specification's reference to the publication.

With further particular regard to claims 34, 35, 39, 40, and 53-55, which recite limitations that the marker is identified as having one or another of the sequences set forth as SEQ ID NOs: 1-14, but which only find support in the material that has been added by this amendment, M.P.E.P. § 608.01(p) does not provide for the incorporation by reference of essential material by reference to non-patent publications. "Essential material" is defined as "that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112)". The sequence of each of the markers is essential information; moreover, its disclosure by the specification is necessary to both describe and enable the claimed invention.

Therefore, if Applicant intends that any information disclosed by the non-patent publications, which are cited, for example, in Table 1 of the specification, including the content of any information identified by reference to the accession number of an electronic database, be relied upon to describe and enable the claimed invention, Applicant is required to amend the specification to include the material incorporated by reference to that publication or database. The amendment must be accompanied by an affidavit or declaration executed by Applicant, or a practitioner representing Applicant, stating that *the amendatory material consists of the same material incorporated by reference in the referencing application*. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

As noted below, until this issue has been resolved, the material added to the claims, which finds support only in the material that has been added to the specification by this amendment, is considered new matter.

Applicant is required to cancel the new matter in the reply to this Office Action, or remedy this issue by other appropriate means.

Grounds of Objection and Rejection Maintained

Specification

5. The objection to the specification, because the use of improperly demarcated trademarks, is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Although Applicant may have made a *bona fide* attempt to resolve this issue by appropriately amending the specification, additional examples of improperly demarcated trademarks appearing in the specification are noted (e.g., Hybond™; see the specification at, e.g., paragraph [0113] of the published application[1]).

Again, appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. The rejection of claims 33-37, 39, 40, and 52-55 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained.

At page 14 of the amendment filed July 18, 2007, Applicant has traversed the propriety of maintaining this ground of rejection, arguing that the amendment to the claims has obviated these issues.

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[1] U.S. Patent Application No. 2004/0023288 A1.

Applicant's argument has been carefully considered but not found persuasive for the following reasons:

Claims 33-37, 39, 40, and 52-55 are directed to a process for detecting cervical dysplasia, cervical cancer, or cervical intraepithelial neoplasia, said process comprising detecting the level of expression $p16^{INK4a}$, detecting the level of expression of a normalization marker characteristic of the presence of ectocervical or endocervical cells, determining the adequacy of the sample by comparing the levels of the normalization markers detected within the sample and threshold levels of the normalization markers, and diagnosing cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia based on the levels of $p16^{INK4a}$ and the adequacy of the sample.

Despite the amendment, claims 33-37, 39, 40, and 52-55 are indefinite for the following reasons:

The claims are directed to an active process that comprises determining the adequacy of the sample by comparing the levels of the normalization markers detected within the samples with threshold levels of the normalization markers and then detecting cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia *based on* the levels of $p16^{INK4a}$ and the adequacy of the sample, but it cannot be ascertained how the determination that the sample is adequate, or not, is made by the comparison step; and furthermore, it cannot be ascertained how cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia is detected upon the "basis" of the level of $p16^{INK4a}$ and the adequacy of the sample. What conclusion must be reached upon comparing the levels of the normalization markers detected within the sample and the threshold levels of the normalization markers, such that it is determined that the sample is adequate? How are the threshold levels of the normalization markers known or determined? Then, what conclusion must be reached upon the "basis" of levels of $p16^{INK4a}$ and the adequacy of the sample, such that the presence of cervical dysplasia, cervical cancer, or cervical intraepithelial neoplasia is detected? What, or how is that "basis" determined?

Given the indeterminacy, uncertainty and/or ambiguity with which the claim defines the invention, it is submitted that the claims fail to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the necessary

degree of clarity and particularity to meet the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. The rejection of claims 33-37, 39, 40, and 52-55 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

As previously noted, the considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

Beginning at page 14 of the amendment filed July 18, 2007, Applicant has traversed the propriety of maintaining this ground of rejection, arguing that the amendment to the claims has obviated these issues.

Applicant's argument has been carefully considered but not found persuasive for the following reasons:

The claims are directed to a process comprising the active steps of detecting the level of at least one "relevant marker characteristic for the presence of cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia in humans" and

"normalization marker characteristic for the presence of ectocervical or endocervical cells".

Without possession of these *markers* and means for detecting their levels, the process cannot be practiced; and absent a detailed and particular description of the markers, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention.

Claim 33, as presently amended, remains generic to any of either plurality of "relevant markers" or "normalization markers"; and although some of the dependent claims are directed to one or more particularly identified polypeptides (i.e., *markers*) by reference to the sequences set forth as SEQ ID NOs: 1-14, none of the claims are directed to both a particularly identified "relevant marker" and a particularly identified "normalization marker".

As explained previously, it is presumed that the claims are directed to one or another genus of polypeptides, which includes members having substantially differing structures and/or functions.

For example, the specification teaches that the genus of "normalization markers" includes a polypeptide identified as "p120". As noted in the preceding Office action, Aho et al. (of record) teaches that the designation "p120" or "p120 catenin (p120ctn)" identifies a plurality of discrete members of a genus of proteins, which owing to alternative splicing and multiple translation initiation codons, includes several isoforms that are expressed from a single gene, which share the central Armadillo repeat domain but have divergent N- and C-termini; see entire document (e.g., the abstract). Aho et al. teaches, though little is known about their specific functions, these structural variants are expected to have non-redundant and quite possible unique roles in cellular biology; see, e.g., the abstract; and page 1391, column 1. Additionally, Aho et al. teaches these variants are differentially expressed in different types of tissues and different types of cells; see, e.g., the abstract.

Thus, following the example provided by the disclosure of Aho et al. it is submitted that it is apparent that the skilled artisan cannot predict whether any one of the presumably different members of polypeptides (e.g., "p120") to which the claims are

directed will be suitable for use in practicing the claimed process because the artisan cannot know whether any species of polypeptide encompassed by the claims will be expressed by the cervical epithelium, or more particularly by the endocervix or ectocervix. Accordingly, the artisan cannot know whether any one species of polypeptide encompassed by the claims can be used as an appropriately suitable normalization marker to identify the presence of endocervical and/or ectocervical cells, or distinguish such cells from other cervical or non-cervical cells, so as to determine the adequacy of the sample. More pointedly, the description is not sufficiently details to permit the skilled artisan to immediately envision, recognize or distinguish which polypeptides encompassed by the claims can be used to practice the claimed process; and therefore the suitability of any such polypeptide for use as a normalization marker in practicing the claimed invention can only be determined empirically.

Though according to claim 35, for example, the at least one "normalization marker" is identified as "SEQ ID NO: 12", which is disclosed by Table 3, at page 29 of the specification, as the amino acid sequence of a polypeptide designated "p120", it is not evident that the remainder of the claims are necessarily limited to a normalization marker that is the polypeptide consisting of this particular amino acid sequence. Might the marker identified in the specification using the nomenclature "p120" be one of the variants disclosed by Aho et al.?

Regardless of whether or not it would be understood that "p120" refers to the polypeptide of SEQ ID NO: 12, and not to any one of the variants described by Aho et al., none of the claims are directed to both a particularly identified "relevant marker" and a particularly identified "normalization marker". So, therefore, because one cannot one immediately envision, recognize or distinguish at least a substantial number of the members of the genus of "relevant markers characteristic for the presence of cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia in humans", or at least a substantial number of the members of the genus of "normalization markers characteristic for the presence of ectocervical or endocervical cells" to which the claims are directed, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention as the time the application was filed.

Applicant is again reminded, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes with the requisite particularity the "markers" (i.e., polypeptides) to which the claims are directed, which can be used in practicing the claimed invention to achieve the claimed result, namely the detection of cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia in human cervical body samples. A description of what a material does, how it might be used or what is must be capable of doing, rather than of what it is, does not suffice to describe the claimed invention.

Considering that fact that the structures and functions of the "normalization markers" may vary so substantially, it is apparent that none of the particularly described markers (e.g., the "p120" polypeptide consisting of the amino acid sequence of SEQ ID NO: 12) is representative of the genus, as a whole; similarly, none of the particularly identified "relevant markers" is reasonably deemed representative of the genus for this same reason.

The only common descriptive feature used to by Applicant to describe members of either plurality of "marker" is that of their usefulness in practicing the claimed invention; however, as explained before, the suitability of any species of polypeptide for use as a "normalization marker" or "relevant marker" in practicing the claimed invention can only be determined empirically, and is not predictable. So, it is again noted that the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Finally, "Guidelines" states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed

invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of polypeptides, which are reasonably presumed to vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

10. The rejection of claims 33-37, 39, 40, and 52-55 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a process for diagnosing cervical dysplasia or cervical cancer, said process comprising detecting the level of expression $p16^{INK4a}$, **does not reasonably provide enablement for using** a process for diagnosing any type of cervical intraepithelial neoplasia, said process comprising detecting the level of expression $p16^{INK4a}$, is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

At page 15 of the amendment filed July 18, 2007, Applicant has traversed the propriety of maintaining this ground of rejection, arguing that the amendment to the claims has obviated these issues.

Applicant's argument has been carefully considered but not found persuasive for the following reasons:

The claims are directed to a process for detecting cervical dysplasia, cervical intraepithelial neoplasia or cervical cancer, said process comprising determining the adequacy of the sample and determining the level of expression $p16^{INK4a}$, which

according to claim 33 is a "marker characteristic for the presence of cervical dysplasia, cervical cancer, or cervical intraepithelial neoplasia".

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the above rejection of the claims, as failing to satisfy the written description requirement, none of the claims are directed to both a particularly identified "relevant marker" and a particularly identified "normalization marker". Furthermore, although examples of each of these pluralities of markers are disclosed, none are representative of the whole of those pluralities, given the degree to which both their structures and functions may vary, so therefore the skilled artisan could not immediately envision, recognize or distinguish at least a substantial number of the members of the genus of "relevant markers characteristic for the presence of cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia in humans", or at least a substantial number of the members of the genus of "normalization markers characteristic for the presence of ectocervical or endocervical cells" to which the claims are directed. Consequently, suitability of any given "marker" (e.g., a polypeptide) for use in practicing the claimed process cannot be predicted but must instead be determined empirically.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify at least one "relevant marker characteristic for the presence of cervical dysplasia, cervical cancer, or cervical intraepithelial neoplasia in human" and at least one "normalization marker characteristic for the presence of ectocervical or endocervical cells", which may be used to practice the claimed process; and yet, presuming that these markers do in fact have some biological function that makes them so suitable for use, it is noted that defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

Further elaborating upon this issue, as explained in the above "written description" rejection, a description of what a material does, how it might be used or what is must be capable of doing, rather than of what it is, does not suffice to describe the claimed invention. Considering the fact that the structures and functions of the "relevant markers" and "normalization markers" may vary so substantially, it appears that the only common descriptive feature used to by Applicant to describe members of either plurality of "marker" is that of their usefulness in practicing the claimed invention; however, as explained before, the suitability of any species of polypeptide for use as a "normalization marker" or "relevant marker" in practicing the claimed invention can only be determined empirically, and is not predictable.

In addition, as explained previously, cervical dysplasia, cervical cancer and cervical intraepithelial neoplasia are distinct conditions or diseases; thus, since $p16^{INK4a}$ is necessarily a marker characteristic for the presence of cervical dysplasia, cervical cancer, **and** cervical intraepithelial neoplasia, it cannot be determined how the active step of detecting cervical dysplasia, cervical cancer, or cervical intraepithelial neoplasia *based on* the levels of $p16^{INK4a}$ and the adequacy of the sample is to be achieved. A marker that does not distinguish cervical dysplasia, cervical cancer, and cervical intraepithelial neoplasia cannot be expected to be useful in the differential diagnosis of such conditions or diseases. If one cannot practice the claimed process to achieve the objective of doing so, i.e., the detection of one or the other of cervical dysplasia, cervical

cancer, and cervical intraepithelial neoplasia in a human cervical body sample, then how might the invention be used without undue and/or unreasonable experimentation? It would seem necessary that the inventive concept be further elaborated in order to develop a means by which cervical dysplasia, cervical cancer, and cervical intraepithelial neoplasia could be distinguished, each from the others; but it does not appear that such a means might be achieved by the sole step of determining the levels of $p16^{INK4a}$ and/or the adequacy of the sample.

In addition, it is aptly noted that while the claims are directed to an active process that comprises determining the adequacy of the sample by comparing the levels of the normalization markers detected in the sample with threshold levels of the normalization markers, the values of the "threshold levels" of the normalization markers to which the claims refer are not known or disclosed. Moreover, it is not immediately apparent how the values of the "threshold levels" of the normalization markers might be known or determined. As such, it is submitted that the claimed invention could not be practiced to achieve the claimed objective of detecting cervical dysplasia, cervical cancer, or cervical intraepithelial neoplasia in a human cervical body sample without undue and/or unreasonable experimentation, since it could not be used without knowledge of the values of these "threshold levels", which are expected to vary widely depending upon the identity of the normalization marker and/or the manner in which the value is determined.

Furthermore, according to the claims, once the determination that the sample is, or is not adequate, then the presence of cervical dysplasia, cervical cancer, or cervical intraepithelial neoplasia is detected on the basis of the levels of $p16^{INK4a}$ and the adequacy of the sample; however, the claims fail to make it clear how the determination of the presence of one or the other of these diseases or conditions is "based" on the level of $p16^{INK4}$ and/or the adequacy of the sample; and therefore it is submitted that the claims fail to describe the process that is regarded as the invention in such a clear and particular manner to reasonably enable the skilled artisan to practice the claimed invention. Moreover, the artisan would not know how the invention is necessarily

practiced, as intended in view of the disclosure, to detect (i.e., diagnose) cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia in humans.

Finally, with further regard to the claimed process, inasmuch as it is allegedly useful for detecting cervical intraepithelial neoplasia in a human cervical body sample, it is again noted that Klaes et al. (of record) teaches the marked overexpression of $p16^{INK4a}$ in all specimens of cervical intraepithelial neoplasm (CIN) I lesions (n = 47) *except* those associated with low-risk HPV types; see entire document (e.g., the abstract). Moreover, although Klaes et al. teaches cervical dysplastic cells, CIN II and CIN III lesions, and cervical carcinoma cells could be identified in the specimens using an antibody that specifically binds $p16^{INK4a}$, no detectable expression as observed in normal cervical epithelium or low-grade cervical lesions (CIN I) associated with low-risk HPV types; see, e.g., the abstract. Accordingly, contrary to the allegations set forth in the specification, there is factual evidence the claimed process cannot be used to diagnose any type of cervical intraepithelial neoplasia, but rather only those types of CIN not associated with low-risk HPV.

At page 15 of the amendment filed July 18, 2007, Applicant has remarked that this last point is incorrect, since in Table 1 (page 279), Klaes et al. provides an indication that of the 15 cases of low-risk HPV type CIN I lesions, 13% had "sporadic stains" and 40% had "focal stains".

In response to these remarks, in the abstract Klaes et al. discloses the following:

> In line with this hypothesis, we observed marked overexpression of $p16^{INK4}$ in all cervical intraepithelial neoplasm (CIN) I lesions (n = 47) except those associated with low-risk HPV types (n = 7) [...]. In contrast, no detectable expression of $p16^{INK4}$ was observed in normal cervical epithelium (n = 42), inflammatory lesions (n = 48) and low-grade cervical lesions (CIN I) associated with low-risk HPV types (n = 7).

Though the table at page 279 appears to indicate that some staining of $p16^{INK4}$ in the specimens of low-risk HPV type CIN I lesions was observed, the staining pattern in those instances is either "sporadic" or "focal". In contrast, Klaes et al. discloses that the staining of pattern of $p16^{INK4}$ in the specimens of high-risk HPV type CIN I lesions, which was observed, was "focal" or, more generally, "diffuse" (Table 1, page 279).

Notably, Klaes et al. discloses that examples of the different patterns of staining are shown in Figure 3 (page 281). A comparison of these different staining patterns suggests that there is a marked difference in the levels at which $p16^{INK4}$ is observed in the different specimens of lesions that have been classified as "$p16^{INK4}$ negative", "sporadic $p16^{INK4}$ positive", "focal $p16^{INK4}$ positive" or "diffuse $p16^{INK4}$ positive".

Again, the claims are directed to a method for detecting cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia in human cervical body samples, which is disclosed as a process that is useful for diagnosing one or the other of these diseases or conditions in humans. Although Klaes et al. may show data in Table 1 that indicates that $p16^{INK4}$ was detected in some specimens of low-risk HPV type CIN I lesions, the conclusion set forth in the abstract might suggest that the observed levels of "sporadic" or "focal" expression was not considered by the authors to be significantly different from the levels of expression observed in any of the cervical specimens of normal epithelium or inflammatory lesions. If there is no significant difference between the level of expression of $p16^{INK4}$ in the specimens of low-risk HPV type CIN I lesions and the levels of expression in specimens of normal epithelium or inflammatory lesions, how might the claimed process be used to distinguish samples comprised of the cells of low-risk HPV type CIN I lesions from samples lacking such cells (e.g., samples composed entirely of normal epithelial cells)?

Klaes et al. teaches it is the *overexpression* of $p16^{INK4}$ in the specimens of high-risk HPV type CIN I lesions, CIN II lesions, CIN III lesions, and invasive cervical carcinomas, as compared to the levels of expression in specimens of normal cervical epithelium, which marks the presence of the cells of these lesions in a specimen of cervical tissue; on the other hand, because $p16^{INK4}$ is not differentially overexpressed in specimens of low-risk HPV type CIN I lesions, Klaes et al. suggests that claimed invention could not be used to detect the presence of the cells of low-risk HPV type CIN I lesions in the samples by distinguishing those cells from normal epithelial cells, merely upon the basis of the levels at which this protein is present in those cells and their normal counterparts.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), there appears to be a preponderance of factual evidence of record that suggests that the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would be insufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

New Grounds of Rejection

Claim Rejections – 35 U.S.C. § 112

11. Claims 33-37, 39, 40, and 52-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 33-37, 39, 40, and 52-55 are indefinite for the following reasons:

(a) Claim 33 recites the limitation, "the levels of the normalization markers detected within the sample solution". This limitation finds no antecedent basis because the preceding body of the claim recites only the steps of preparing a sample solution and determining the levels of at least one relevant marker and at least one normalization marker, but not necessarily the levels of the normalization markers within the sample solution; moreover, the process comprises *determining* the level of at least one normalization marker, as opposed to "detecting" the level.

(b) Claim 33 recites the limitation, "the positive level of the relevant marker"; however, this limitation finds no antecedent basis in the preceding language of the claim and it cannot be ascertained to which "positive level of the relevant marker" the claim refers.

For these reasons, it is submitted that the claims fail to delineate the subject matter that is regarded as the invention with the clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, so as to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

12. Claims 33-37, 39, 40, and 52-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

Claims 34, 35, 39, 40, and 53-55 recite limitations that the marker is identified as having one or another of the sequences set forth as SEQ ID NOs: 1-14; however, it appears that the language of the claims, as presently amended, only finds support in the material that has been added by this amendment.

Applicant has contended support for the material added to the specification is found in a printout from the NCBI website, which is attached to the amendment filed July 18, 2007.

However, written support for the material added to the specification must be found in the specification, including the claims, as originally filed; in this instance, it is not immediately apparent where in the specification, as filed, that support may be found.

What nexus between the material, which has not been added to the specification, and information extracted from the NCBI website is found in the specification, as filed?

It is noted, for example, that while it may be Applicant's position that written support for the addition of the sequence set forth as SEQ ID NO: 9 may be found in the non-patent publication cited in Table 1 (page 21 of the specification, as filed), this disclosure and reference to this publication does not appear to provide support for the added material because it does not *particularly* identify the added material.

According to M.P.E.P. 608.01(p):

> Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. *In re de Seversky*, 474 F.2d 671, 177 USPQ 144 (CCPA 1973).

With regard to incorporation by reference, the Federal Circuit in deciding *Advanced Display Systems Inc. v. Kent State University,* 54 USPQ2d 1673 (CA FC), has further opined:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. *See In re Seversky,* 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-03, 170 USPQ 213, 216-17 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order have that material considered part of a later application); *cf. Lund*, 376 F.2d at 989, 153 USPQ at 631 (holding that a one sentence reference to an abandoned application is not sufficient to incorporate material from the abandoned application into a new application). Whether and to what extent material has been incorporated by reference into a host document is a question of law. *See Quaker City Gear Works, Inc. v. Skil Corp.*, 747 F.2d 1446, 1453-54, 223 USPQ 1161, 1166 (Fed. Cir. 1984) (reasoning that whether a document is incorporated by reference into a patent presents a question of law when determining enablement). *Id.* at 1679-1680.
>
> [Thus] the standard of one reasonably skilled in the art should be used to determine whether the host document describes the material to be incorporated by reference with sufficient particularity. *Id.* at 1680.

In this instance, the disclosures and references cited in Table 1, for example, might be deemed to provide support for the added material *upon proper incorporation by reference of the specific material, which has been added*, but then only if that amendatory material may be unambiguously identified, upon a reading of the publication, as the particular material that was intended to have been incorporated by the original specification's reference to the publication.

Then, as an additional matter, M.P.E.P. § 608.01(p) does not provide for the incorporation by reference of essential material by reference to non-patent publications. "Essential material" is defined as "that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe

the best mode (35 U.S.C. 112)". The sequence of each of the markers is essential information; moreover, its disclosure by the specification is necessary to both describe and enable the claimed invention.

Therefore, if Applicant intends that any information disclosed by the non-patent publications, which are cited, for example, in Table 1 of the specification, including the content of any information identified by reference to the accession number of an electronic database, be relied upon to describe and enable the claimed invention, Applicant is required to amend the specification to include the material incorporated by reference to that publication or database. The amendment must be accompanied by an affidavit or declaration executed by Applicant, or a practitioner representing Applicant, stating that *the amendatory material consists of the same material incorporated by reference in the referencing application.* See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

However, until this issue is resolved by properly amending the specification to provide the necessary written support for the language of the claims, the amendment filed July 18, 2007, is deemed to have introduced new matter, thereby violating the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Conclusion

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
Stephen L. Rawlings, Ph.D.
Primary Examiner
Art Unit 1643

slr
September 25, 2007